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Prealbumin is as important as albumin in the nutritional assessment of hemodialysis patients

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Prealbumin is as important as albumin in the nutritional assessment of hemodialysis patients.

Background. Although serum prealbumin is considered a valid indicator of nutritional status in hemodialysis patients, there is relatively little evidence that its determination is of major prognostic significance. In this study, we aimed to determine the independent association of serum prealbumin with survival in hemodialysis patients, after adjusting for serum albumin and other indicators of protein energy nutritional status.

Methods. Serum prealbumin was measured in more than 1600 maintenance hemodialysis patients. We determined the correlations among prealbumin and other indicators of nutritional status, including serum albumin, and bioimpedance-derived indicators of body composition. The relationship between serum prealbumin and survival was determined using proportional hazards regression.

Results. The serum albumin was directly correlated with the serum prealbumin ($r = 0.47$, $P < 0.0001$), but still explained <25% of the variability in prealbumin. Prealbumin was inversely related to mortality, with a relative risk reduction of 6% per 1 mg/dL increase in prealbumin, even after adjusting for case mix, serum albumin, and other nutritional indicators. The increase in risk with lower serum prealbumin concentrations was observed whether the serum albumin was high or low.

Conclusion. In hemodialysis patients, the serum prealbumin provides prognostic value independent of the serum albumin and other established predictors of mortality in this population.

Protein energy malnutrition (PEM) affects more than 50% of maintenance dialysis patients and is unequivocally associated with morbidity and mortality. Whether related to diminished dietary intake, inflammation, adequacy of dialysis, socioeconomic factors, or a combination thereof, patients with evidence of PEM have a relative risk (RR) of death between two- and tenfold or more, depending on the severity of PEM and the interaction of PEM with other factors (age, anemia, dialysis vintage, etc.) [1–3]. Serum albumin has been the most commonly employed marker of PEM, based largely on the statistical association between diminished serum albumin, mortality, and morbidity. Indeed, the Health Care Financing Administration's (HCFA) core clinical indicators for adequate dialysis treatment involves an audit of serum albumin concentration in dialysis facilities [4] coequal with anemia and measures reflecting the adequacy of dialysis.

The clinical approach to the patient with PEM within the dialysis facility is ideally multidisciplinary, with nephrologist and renal dietitian collaborating to address the patient's underlying remediable medical conditions as well as ensuring that dietary intake is adequate to meet metabolic needs. Identification of patients at risk is an essential part of quality care attempting to abrogate the burden of PEM in the maintenance dialysis population. However, a thorough understanding of the underlying pathophysiology(s) of PEM in dialysis patients is lacking, including the relative contributions of dietary intake and inflammation. There is no uniform agreement about appropriate therapy for this condition. An improved understanding of the cause(s) and consequences of PEM is required to enhance quality of care for dialysis patients. Such an understanding necessarily includes a thorough understanding of the markers of PEM and their prognostic significance.

As part of the National Kidney Foundation Dialysis Outcomes Quality Initiative (NKF-DOQI) Practice Guideline on Nutrition, the validity and clinical utility of several indicators of PEM, including prealbumin (also known as transthyretin), were subject to a thorough, evidence-based literature review [5]. Prealbumin was deemed a valid and clinically useful indicator of PEM in maintenance dialysis patients by the NKF-DOQI panel. How-

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ever, the quantity of evidence linking prealbumin to PEM and to morbidity and mortality was small relative to the evidence for other biochemical markers, such as serum albumin and creatinine [6–10]. There were several important questions regarding prealbumin that remained unanswered. First, the goal serum prealbumin concentration was unknown. Published reports had stratified patients above and below 30 mg/dL, a value well within the normal range for nonuremic adults [6–10]. Second, since prealbumin concentration is partly dependent on glomerular filtration, there was concern that confounding by renal function would limit its specificity, particularly among incident dialysis patients with residual renal function. Finally, while some investigators had suggested that prealbumin might be superior to albumin as an individual predictor of mortality in dialysis, it was not known whether there was marginal predictive power once serum albumin was accounted for, and if so, whether the added value of prealbumin was restricted to patients with high or low serum albumin concentrations. We therefore undertook the following analyses in an effort to answer these inquiries.

METHODS

Study subjects

Study subjects were 3009 prevalent adult hemodialysis patients from 101 free-standing Fresenius Medical Care North America (FMCNA) dialysis units across the United States. Inclusion criteria included age ≥18 years and three times weekly in-center hemodialysis for ≥3 months. Patients with an amputation above the transmetatarsal site were excluded from participation. Bioelectrical impedance analysis (BIA Quantum; RJL Systems, Inc., Clinton Twp., MI, USA) was performed before a midweek dialysis session during the first six months of 1995. Weight was obtained before dialysis. Details of the BIA examination are provided elsewhere [11]. Resistance and reactance in ohms was obtained directly from the BIA device. Phase angle was calculated in radians and multiplied by $180/\pi$ ($\sim$3.14159265) to covert radians to degrees. Reactance, resistance, phase angle, and the derived estimates of total body water (TBW) and body cell mass (BCM) were merged with the Patient Statistical Profile, a database with selected demographic, historic, and laboratory information on patients cared for at FMCNA-affiliated dialysis facilities. Laboratory values were means of the three months proceeding BIA testing. Serum albumin was measured using the bromocresol green method. Serum prealbumin was measured using immunoprecipitin analysis. The duration of follow-up after BIA testing ranged from 2 days to 18 months. Patients whose survival time was unknown or uninterpretable (N = 19, 0.6%) were excluded from the analysis.

Statistical analysis

Continuous variables were expressed as mean ± SD and compared with Student's t-test, the Wilcoxon rank sum test, or analysis of variance (ANOVA) where appropriate. Correlation among variables was described with the Pearson product moment correlation coefficient. Categorical variables were described using proportions and were analyzed with the χ^2 test. Prealbumin was analyzed as a continuous variable and in categories determined a priori of 5 mg/dL increments (<20, 20 to 25, 25 to 30, 30 to 35, >35 mg/dL). Unadjusted and multivariable analyses [adjusted for age, gender, race or ethnicity, diabetes, vintage (time since initiation of dialysis), albumin, creatinine, dialysis dose, hemoglobin, ferritin, body size, and phase angle] were conducted to explore the association between prealbumin concentration and survival. Multivariable regression was performed using the proportional hazards ("Cox") model, with variable entry and exit criteria set at the $P = 0.05$ level [12]. Plots of log [−log (survival rate)] against log (survival time) were performed to establish the validity of the proportionality assumption [13]. Multiplicative interaction terms were tested to explore interaction among prealbumin concentration and selected explanatory variables. An indicator variable for "missing" prealbumin was included in all regression models. Stratified analyses were conducted among subjects below and above the median serum albumin concentration to determine whether the association between prealbumin and survival was albumin dependent. Unadjusted and multivariable RRs and 95% confidence intervals (95% CI) were calculated based on model parameter coefficients and standard errors, respectively. Patients who underwent kidney transplantation (N = 82, 2.7%), recovered renal function (N = 18, 0.6%), transferred dialysis facilities (N = 287, 9.7%), withdrew from dialysis (N = 42, 1.3%), or were lost to follow-up for unknown reasons (N = 8, 0.3%) were censored. Subjects with and without prealbumin values were compared to evaluate whether missing data for this variable were missing roughly at random. Two-tailed P values of less than 0.05 were considered statistically significant. Statistical analyses were conducted using SAS 6.12 (SAS Institute, Cary, NC, USA).

RESULTS

The mean age was 60.5 ± 15.5 years; the demographics were 47.2% of the patients were women, 46.9% were black, 45.4% were white, 6.5% were Hispanic, 1.2% were of another race or ethnicity, and 36.5% had diabetes. Table 1 shows the baseline demographic, laboratory, and body composition (by BIA) characteristics of patients with (N = 1618, 54%) and without (N = 1372, 46%) serum prealbumin values. Fewer African Americans and more Caucasians were tested ($P < 0.0001$). The mean

Table 1. Demographic, laboratory, and body composition data on patients with and without prealbumin measurements

	Prealbumin +	Prealbumin −	*P* value
Age *year*	60.8 ± 15.2	60.0 ± 15.7	0.16
Sex *% female*	46.8%	48.5%	0.16
Race or ethnicity			<0.0001
Caucasian	47.5%	43.0%	
African American	43.2%	51.2%	
Hispanic	8.1%	4.6%	
Other	1.2%	1.2%	
Diabetes %	35.7%	37.5%	0.29
Vintage *years*	3.9 ± 3.6	3.8 ± 3.8	0.32
Height *cm*	166.9 ± 11.4	167.0 ± 11.1	0.91
Weight *kg*	74.3 ± 18.6	74.3 ± 18.5	0.94
Creatinine *mg/dL*	10.8 ± 3.6	10.9 ± 3.5	0.72
Pre-dialysis BUN *mg/dL*	68.2 ± 17.1	67.2 ± 17.4	0.11
Albumin *g/dL*	3.86 ± 0.36	3.84 ± 0.36	0.27
Cholesterol *mg/dL*	175.7 ± 46.6	177.0 ± 44.3	0.44
Bicarbonate *mEq/L*	20.2 ± 2.8	20.6 ± 2.9	0.0003
Hemoglobin *g/dL*	10.4 ± 1.1	10.2 ± 1.1	<0.0001
Ferritin *μg/L*	290 (143 to 591)	242 (108 to 470)	<0.0001
URR *%*	65.4 ± 7.1	65.4 ± 6.9	0.99
Kt/V	1.08 ± 0.21	1.08 ± 0.21	0.93
Kt *L*	43.3 ± 9.8	43.3 ± 9.3	0.96
Resistance *Ω*	498.2 ± 94.4	497.2 ± 100.1	0.79
Reactance *Ω*	40.0 ± 13.7	41.9 ± 13.8	0.0002
Phase angle *degrees*	4.71 ± 1.74	4.94 ± 1.79	0.0004
TBW *kg*	40.8 ± 9.4	40.8 ± 9.1	0.83
BCM *kg*	26.0 ± 5.8	26.3 ± 5.8	0.17

Abbreviations are: BUN, blood urea nitrogen; URR, urea reduction ratio; TBW, total body water estimated by BIA; BCM, body cell mass estimated by BIA. *N* = 1618 and 1372 in prealbumin + and prealbumin − groups, respectively.

Table 2. Patient characteristics by prealbumin category

	<20	20–25	25–30	30–35	>35	*P* value
Age *year*	65.1	62.4	61.0	58.1	55.0	<0.0001
Sex *% female*	50.6	51.7	45.7	41.3	35.0	0.002
Race or ethnicity						0.001
Caucasian	64.6	52.7	45.3	40.7	29.3	
African American	31.7	38.9	43.0	50.7	57.1	
Hispanic	2.9	7.6	10.4	7.7	10.7	
Other	0.8	0.8	1.4	0.9	2.9	
Diabetes *%*	46.4	39.4	35.5	27.4	27.9	0.001
Vintage *year*	3.79	3.90	3.94	3.93	3.70	0.96
Height *cm*	166.2	165.9	166.8	168.2	168.4	0.03
Weight *kg*	70.0	72.9	75.1	75.3	79.7	<0.0001
Creatinine *mg/dL*	8.3	10.0	10.9	12.2	13.4	<0.0001
BUN *mg/dL*	58.5	64.8	68.6	73.6	79.2	<0.0001
Albumin *g/dL*	3.57	3.77	3.89	4.00	4.13	<0.0001
Cholesterol *mg/dL*	151.8	169.8	178.2	186.9	195.2	<0.0001
Bicarbonate *mEq/L*	20.8	20.4	20.1	20.0	19.3	<0.0001
Hemoglobin *g/dL*	10.1	10.1	10.5	10.6	10.6	<0.0001
Ferritin *μg/L*	418	416	433	446	530	0.16
URR *%*	64.3	65.6	65.4	65.8	65.2	0.13
Kt/V	1.05	1.09	1.08	1.09	1.07	0.23
Kt *L*	41.1	42.8	43.1	44.4	45.8	<0.0001
Resistance *Ω*	505.4	494.8	502.1	500.9	473.6	<0.0001
Reactance *Ω*	34.5	37.2	40.2	43.9	46.6	<0.0001
Phase angle *degrees*	4.07	4.41	4.67	5.13	5.79	<0.0001
TBW *kg*	39.7	40.2	40.7	41.5	43.6	0.0007
BCM *kg*	24.4	25.1	25.8	27.2	28.4	<0.0001

Abbreviations are: BUN, blood urea nitrogen; URR, urea reduction ratio; TBW, total body water estimated by BIA; BCM, body cell mass estimated by BIA. *N* = 237, 383, 519, 339, and 140 in <20, 20–25, 25–30, 30–35, ≥35 mg/dL groups. The *P* value refers to overall analysis of variance (ANOVA).

hemoglobin and serum ferritin values were slightly higher, and the bicarbonate, reactance, and phase angle by BIA values were slightly lower in the group whose prealbumin was tested. These differences persisted after adjusting for the imbalance in race or ethnicity. Overall, there were few statistically significant or clinically meaningful differences in the tested and nontested groups, indicating little overt bias in prealbumin test ordering. In other words, prealbumin was not ordered exclusively in subjects with low serum albumin or other nutritional or related disorders.

The mean serum prealbumin was 26.6 ± 6.4 mg/dL (median 26.8, interquartile range 22.6 to 30.9, full range 2.8 to 52.3 mg/dL) and was normally distributed (Wilk-Shapiro χ^2, $P = 0.97$). Prealbumin was directly correlated with all nutritional indicators, including serum albumin ($r = 0.47$), creatinine ($r = 0.42$), predialysis blood urea nitrogen ($r = 0.34$), cholesterol ($r = 0.26$), predialysis body weight ($r = 0.13$), reactance ($r = 0.27$), phase angle ($r = 0.27$), TBW ($r = 0.10$), and BCM ($r = 0.20$), and inversely correlated with age ($r = -0.18$, $P < 0.0001$ for all Pearson *r* values). While the correlation with serum albumin was relatively high, it was far from 1.0. Indeed, with a correlation of 0.47, less than one fourth of the variability in serum prealbumin can be explained by the serum albumin concentration.

Prealbumin was categorized a priori into the following five groups: <20, 20 to 25, 25 to 30, 30 to 35, and ≥35 mg/dL (corresponding to 14.6, 23.7, 32.1, 21.0, and 8.7% of the tested population). Table 2 displays patient characteristics within the five prealbumin categories. It is noteworthy that women, Caucasians, and persons with diabetes were underrepresented in the higher prealbumin categories. Indeed, the prealbumin concentration was significantly lower among women (26.0 vs. 27.2 mg/dL in men, $P = 0.0002$), Caucasians (25.4 vs. 27.9 mg/dL in nonwhites, $P < 0.0001$), and persons with diabetes (25.5 vs. 27.3 mg/dL in persons without diabetes, $P < 0.0001$).

Prealbumin and mortality

The unadjusted RR of death was 0.91 (95% CI, 0.90 to 0.93) per mg/dL increase in prealbumin concentration. In other words, there was a 9% decrease in the risk of death for each 1 mg/dL increase in the serum prealbumin concentration. The RR of death was attenuated slightly (RR 0.92, 95% CI 0.90 to 0.94) after adjustment for case mix (that is, age, gender, race, diabetes, vintage). Even after forcing serum albumin, creatinine, hemoglobin, ferritin, phase angle, Kt (or URR and URR^2), and body weight (or Quetélet's index or TBW) into the model, the association between serum prealbumin and mortality remained statistically significant (RR 0.94, 95% CI, 0.92

Table 3. Unadjusted, case mix-adjusted, and multivariable-adjusted RR (and 95% CI) of death by prealbumin category

Prealbumin	Unadjusted	Case-mix adjusted	Multivariable-adjusted
<20 mg/dL	4.42 (2.81 to 6.97)	3.43 (2.17 to 5.43)	2.58 (1.59 to 4.16)
20–25 mg/dL	2.03 (1.27 to 3.24)	1.71 (1.07 to 2.73)	1.51 (0.94 to 2.44)
25–30 mg/dL	1.14 (0.70 to 1.85)	1.00 (0.62 to 1.63)	0.95 (0.59 to 1.55)
30–35 mg/dL	1.00	1.00	1.00
≥35 mg/dL	0.77 (0.35 to 1.70)	0.90 (0.41 to 2.00)	0.98 (0.47 to 2.16)

N = 237, 383, 519, 339, and 140 in <20, 20–25, 25–30, 30–35, and ≥35 mg/dL groups. Relative rate (RR) and 95% CI are derived from proportional hazards regression analysis using the 30–35 mg/dL group as the referent.

to 0.96). The designation of "missing" prealbumin values was not associated with death risk ($P = 0.55$).

Serum albumin and prealbumin were placed into models together to compare their relative predictive power. In unadjusted, case mix-adjusted, and multivariable-adjusted models, including only those patients with prealbumin values, the χ^2 associated with the prealbumin term was higher, indicating explanation of a larger fraction of the variance (unadjusted χ^2 39.6 vs. 5.1, case mix adjusted χ^2 26.2 vs. 2.8, multivariable adjusted χ^2 22.5 vs. 1.9, prealbumin vs. albumin). In the latter two instances, serum albumin lost its conventional statistical significance with inclusion of the prealbumin term.

Since serum albumin and prealbumin are both reflective of the visceral protein pool and acute phase reactants, we explored whether the prealbumin-mortality relationship was dependent on albumin. In other words, we inquired whether the association between prealbumin and mortality was restricted to individuals with low or high serum albumin concentrations. Indeed, the association between prealbumin and mortality was not dependent on the albumin concentration. The RRs of death per 1 mg/dL increase in prealbumin were 0.92 and 0.93 in patients with serum albumin concentrations above and below the median, respectively. Moreover, the relationship between prealbumin and mortality was not influenced by age, gender, race, diabetes, or vintage (multiplicative interaction term P values, 0.11 to 0.73).

To test the linearity assumptions applied previously in this article, we evaluated the serum prealbumin concentration in five categories: <20, 20 to 25, 25 to 30, 30 to 35, and ≥35 mg/dL. These categories were chosen to provide sufficient power within categories to assess risk relative to the "goal" prealbumin concentration (>30 mg/dL) proposed by Avram et al [6–9]. The unadjusted, case mix-adjusted, and multivariable-adjusted RRs and 95% CIs for each prealbumin category (relative to 30 to 35 mg/dL) are listed in Table 3. Since the serum albumin and prealbumin concentrations were directly correlated, adjustment for serum albumin in multivariable regression models sharply reduced the significance level for each prealbumin category relative to the referent category. If one considered a prealbumin "cut-off" of 25 mg/dL rather than 30 mg/dL, the multivariable RR of death for patients with prealbumin <15, 15 to 20, and 20 to 25 mg/dL were all significantly increased (RR 2.80, 95% CI 1.62 to 4.82, RR 2.48, 95% CI 1.70 to 3.62, and RR 1.53, 95% CI 1.07 to 2.17).

To evaluate whether prealbumin was less specific as a nutritional indicator among patients with residual renal function, we stratified patients by vintage (above and below the median of 2.6 years), assuming that residual renal function would be negligible in most patients after this time. Unadjusted, case mix-adjusted, and multivariable-adjusted RRs for serum prealbumin were significant in both subgroups (data not shown), suggesting that the effect of prealbumin was not excessively confounded by residual renal function.

DISCUSSION

These studies confirm that serum albumin and prealbumin are directly correlated, but that each explains <25% of the concentration of the other. Furthermore, these studies suggest that the serum prealbumin concentration may be more closely associated with mortality than serum albumin, the current standard indicator of PEM [4, 14]. Based on these findings, one might ask whether prealbumin should be used as the standard, rather than albumin. More reasonably, both seem to provide complementary information regarding PEM, just as serum albumin and creatinine concentrations do. In any case, it has become clear that a more in-depth understanding of the cause(s) of and potential therapies for PEM in dialysis patients will be required in order to improve clinical outcomes. Such investigations would seem the responsibility of institutional providers, academic medical centers, and governments, rather than dialysis facilities per se.

Prealbumin, also known as transthyretin, is a 54,000 D protein synthesized primarily by the liver. Its main function is to transport thyroxine and indirectly vitamin A, as it serves as a carrier protein for retinol binding protein [15]. In humans, prealbumin has been shown to increase with increases in protein and calorie intake and to decrease when protein intake is inadequate [15]. As with serum albumin, prealbumin has been shown to decrease in the face of acute or chronic inflammation (that is,

"acute phase reactant"), limiting its specificity as a marker of nutritional intake. In contrast to serum albumin, however, its half-life is relatively short (~2 to 3 days). It has therefore been suggested that prealbumin may be a more sensitive indicator of nutritional status than either serum albumin or transferrin [16].

Much of the clinical research linking serum prealbumin to mortality in dialysis patients has been performed by Avram et al [6–9]. In their most recent report, Sreedhara et al found that a serum prealbumin <30 mg/dL at the initiation of dialysis was associated with an increased risk of death in 111 hemodialysis (RR = 2.6, $P = 0.002$) and 78 peritoneal dialysis patients (RR = 1.8, $P = 0.035$) followed over five years. The association between prealbumin and mortality remained significant in the larger hemodialysis group after adjusting for the effects of age and diabetes in a multivariable model. It is noteworthy that Sreedhara et al found that inclusion of prealbumin in the mortality model extinguished the significance of the serum albumin term, as we have also confirmed. These investigators and others [17] have shown the correlation between serum albumin and prealbumin to be in the range of $r = 0.5$.

Two small studies have examined the effects of nutrition support on serum prealbumin values. Vehe et al provided nutrition support (~34 kcal/kg/day and 1.3 g protein/kg/day) to 14 patients with chronic renal failure and examined the change in serum levels of insulin growth factor-1 (IGF-1), fibronectin, and prealbumin from baseline at seven and 28 days [18]. Prealbumin increased significantly from 15.3 ± 7.8 to 24.6 ± 19.0 mg/dL by day 28 ($P < 0.01$). Cumulative nonprotein calories ($r = 0.37$, $P < 0.01$) and cumulative protein intake ($r = 0.43$, $P < 0.01$) were directly correlated with serum prealbumin. More recently, Mortelmans et al showed a nonsignificant increase in serum prealbumin in 16 patients given intradialytic parenteral nutrition over a nine-month period [19]. Larger studies are clearly needed to determine whether prealbumin is a suitable parameter to follow after initiation of nutrition support.

There are several limitations to this analysis. First, the sample was restricted to hemodialysis patients so that the role of prealbumin in peritoneal dialysis patients or in individuals with advanced chronic renal insufficiency could not be evaluated. Second, all-cause mortality was the only outcome evaluated. Additional information on cause-specific mortality (for example, death due to infection, cardiovascular disease), morbidity, functional status, and health-related quality of life would have been of interest. Third, residual renal function was not directly measured, and the use of vintage to stratify patients by their degree of residual renal function has not been validated. Fourth, prealbumin was not measured longitudinally so that the estimated effect on mortality of a change in serum prealbumin could not be evaluated. Finally, the sample size was relatively small so that the power to explore potential interactions among prealbumin, demographic factors, and indicators of nutritional status was limited.

In summary, serum prealbumin was normally distributed in more than 1600 maintenance hemodialysis patients, with a mean value of 26.6 mg/dL. As with serum albumin, values well within the reference range (18.0 to 33.8 mg/dL; Lifechem Laboratories, Rockleigh, NJ, USA) were associated with a significantly increased risk of death. The serum prealbumin stratified mortal risk at least as well as serum albumin when both variables were included simultaneously in multiple regression models. There was a graded change in the RR of death (multivariable linear estimate 6% increase in risk per 1 mg/dL decrease in prealbumin) by prealbumin concentration. The risk of death was unambiguously increased among individuals with serum prealbumin <25 mg/dL, even after adjusting for serum albumin, case mix, and other established predictors of death in hemodialysis patients. While there was insufficient power to demonstrate a significant difference among the 25 to 30 mg/dL, 30 to 35 mg/dL, and >35 mg/dL groups (in part because of collinearity between albumin and prealbumin), there is reason to believe that higher values would be associated with lower risk, based on the unadjusted analyses and linear trends presented here. While any recommendations for the routine use of prealbumin must take into account the costs of laboratory testing along with the likelihood of affecting change after identification of an abnormality, these data answer some of the questions (vide supra) regarding the validity of serum prealbumin (transthyretin) in hemodialysis patients and provide compelling evidence for its providing added value in nutritional assessment. Longitudinal analyses exploring the specificity of prealbumin for PEM, its sensitivity to change, and its performance relative to albumin and other serum proteins will be necessary to define better its role in nutritional (and inflammatory) assessment and therapy in end-stage renal disease.

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